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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,811	05/14/2001	Robert E. Reiter	30435.69USD2	9472

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,811	REITER ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2002 and 19 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-56 and 58-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-56 and 58-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group II, claims 53-56, 58-73 in paper number 11 is acknowledged. The traversal is on the ground(s) that claims 53-56 and 58-73 fall within the invention of Group II and cancellation of claims 1 and 57 and amendments to claims 58-72 render the restriction requirement moot. This is found persuasive and claims 53-56 and 58-73 are all within Group II claims.

2. Upon further consideration the species requirement is withdrawn.

3. Claims 53, 56 have been amended and claims 74-76 have been added in the amendment filed 11/19/02.

4. Claims 53-56, 58-76 are under examination.

5. NOTE: The amendment filed 5/14/01 states that support for claim 53 can be found in specification 09/564,329 at pages 19, 22, 27, 47, 89, and figures 6, 9-11, 20-32, and 62-64. Upon review of the specification of the instant application and 09/564,329 support for claims 53-56, 58-73 is found on pages 5, lines 18-20, and page 60, lines 9-16.

Specification

6. The disclosure is objected to because of the following informalities:

a. The first line of the specification should be updated to indicate the U.S. Patent numbers for applications 09/251835, 09/203939, 09/318503, and 09/038261.

b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, for example, A method for inducing an immune response having a cancer expressing PSCA.

c. The Brief Description of the Drawings, pages 6-18, is incomplete as it lacks a separate description for the Figures (for example Figure 1 should be Figure 1A and 1B. The Brief Description of the Drawings need to be amended so that Figures recite separate descriptions for each view that match the labels for the Drawings. Also any reference to the figures in the specification needs to be amended accordingly.

d. The address of the ATCC on page 28, line 3 needs to be updated. The new address is: 10801 University Boulevard, Manassas, VA 20110-2209.

e. The specification should be updated to include all SEQ ID Nos for all sequences in the specification. For example those listed on page 30, line 26 and those contained in the figures and described in the Brief Description of the drawings.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 53-56, 58-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 53-56, 58-67 are indefinite for reciting "a method of inducing an immune response in a subject" because the exact meaning of the phrase is not clear. What is the immune response directed against? Is the immune response directed against SEQ ID NO:2 or 4 in claim 53 or SEQ ID NO:2 in claim 75 or some other antigen?

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 53-56, 58-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are to methods of inducing an immune response in a subject having a cancer expressing a PSCA protein or cells that express PSCA. The specification teaches PSCA of SEQ ID NO:2 (Figure 1B) of human and SEQ ID NO:4 (Figure 3) of mouse. The specification teaches PSCA as "includes all naturally occurring allelic variants, isoforms" and those that encompass proteins with conservative substitutions (see page 20, line28 to page 21, line 27). With the exception of SEQ ID NO:2 and 4 the specification and the art of record does not disclose any variants as broadly claimed. In addition there is no art of record that describes the functional characteristics of a

PSCA protein for one skill in the art to envisage what is necessary for the protein to be characterized as a PSCA protein. In addition, as indicated in Figure 3, while there is homology between the mouse and the human PSCA, there is no structural or functional characteristics that distinguish a PSCA protein.

The general knowledge in the art concerning variants does not provide any indication of how the structure of one variant is representative of unknown variants. Reiger et al. (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:2 and 4 the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

11. Claims 53-56, 58-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing an immune response against the protein of SEQ ID NO:2 in a human cancer patient that expresses the protein of SEQ ID NO:2 or cells that express SEQ ID NO:2, wherein the method comprises administration of residues 1 to 123 of SEQ ID NO:2 or a method for inducing

an immune response against SEQ ID NO:4 in a mouse that expresses the protein of SEQ ID NO:4 wherein the method comprises administration of residues 1 to 123 of SEQ ID NO:4, does not reasonably provide enablement for a method of inducing an immune response against just any antigen in just any subject by administration of just any portion of SEQ ID NO:2 or 4 or a method of inducing an anti-tumor response in any subject with just any fragment of SEQ ID NO:2 or 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of inducing an anti-tumor immune response to any antigen in any cancer subject that expresses PSCA or cells that express PSCA wherein the method comprises administration of any portion of SEQ ID NO:2 or 4 or specific regions of SEQ ID NO:2 wherein the subject is a sheep, rat, dog, cat, pig, house, human, or mouse. The claims encompass administration of any fragment of SEQ ID NO:2 or 4 to any subject for inducing an anti-tumor response. For example the claims encompass administration of any fragment of SEQ ID NO:2 to a

sheep, rat, dog, cat, pig, house which has not been shown to express human PSCA or mouse PSCA or a protein highly homologous to such for an anti-tumor response.

The specification teaches the human PSCA protein of SEQ ID NO:2 and the mouse PSCA protein of SEQ ID NO:4. The specification discloses PSCA protein or fragments for use as a tumor antigen in a vaccine for generating a humoral and cell-mediated immunity for anti-cancer therapy (see page 60). In addition, the claims encompass administration of specific fragments of SEQ ID NO:2 or any portion of SEQ ID NO:4 wherein the specification does not teach that just any fragment of SEQ ID NO:2 can be used in humans to induce an anti-tumor response or just any fragment of SEQ ID NO:4 in mice.

Since the therapeutic indices of immunotherapeutic regimens can be species- and model-dependent, it is not clear that reliance on the generation of disclosing certain antigen specificities of antigens on certain tumor cell lines or tumor cells accurately reflects the relative ability of the claimed methods to make such compositions to treat tumorous disease, encompassed by the claims.

There is insufficient guidance and direction to prepare tumor adjuvant vaccines using any PSCA-antigen-derived peptide. The claims encompass administering fragments of SEQ ID NO:2 or 4 and it is well known that not every fragment of a protein can be used to produce antibodies or produce an anti-tumor response that is encompassed in the claims. While an antibody can be made to any fragment of a protein not every fragment would produce an immune response that would result in an anti-tumor response. Due to the location of the fragment in the properly folded protein

only those that would be recognized on the surface of the protein could be used for anti-tumor responses.

For example, (Spitler, Cancer Biotherapy, 1995; page 1, column 1, paragraph 1); "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response".

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (J. NIH Research, 1995; see entire document, particularly the last paragraph). It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Furthermore, no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (Ezzell; page 48, paragraph 6). In addition, both Spitler and Ezzell teach that the entire protein was used as a vaccine not just any fragments of the proteins.

Therefore, the skilled artisan at the time the invention was made recognized the lack of predictability of the nature of the art and state of the prior art to which the instant

invention pertains. Also, such disclosures clearly indicate that the amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 53-55, 73, 74-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Au-Young (U.S. Patent 5,856,136, filed 7/96) and further in view of Spitler (U.S. Patent 5,738,867, filed 6/95).

Claim 73 is included in this rejection because claim 73 is granted the priority date of 12/98 where the first instance of bladder cancer was observed to be disclosed in 09/203939.

The claims recite a method of inducing an immune response in a human that has bladder cancer by administering residues 1 to 123 of SEQ ID NO:2 and a method of producing an antibody by such method.

Au-Young teach the SCAH-2 protein SEQ ID NO:2 (see column 2, lines 14-16 and 44-50, column 14, lines 22-32). Au-Young also teach antigenic peptides of the protein (see columns 13-14). The SCAH-2 protein of AU-Young is the identical protein as PSCA in the instant invention (see SEQ ID NO:2 in Au-Young patent as compared to SEQ ID NO:2 in the instant application) except at amino acid 94. SEQ ID NO:4 of Au-Young is the DNA that encodes SEQ ID NO:2 of Au-Young. At nucleotide 296 the nucleotide in SEQ ID NO:4 is a "S". Standard IUB meaning for this convention is that this nucleotide is a "G" or a "C". The codon for the amino acid sequence of SEQ ID NO:2 of Au-Young at position 94 is listed as a "X" but if nucleotide 294 is a "C" then the codon would code for Alanine and if the nucleotide at 294 is a "G" this would be a

glycine (see the genetic code at page 41 of Watson et al (Recombinant DNA, Scientific American Books, 1992). Thus, Au-Young teach a sequence identical to SEQ ID NO:2 of the instant application. Au-Young teach the protein of SEQ ID NO:2 was observed in bladder tumor (see column 4, lines 29-30). Au-Young does not teach a method of inducing an immune response in a human patient by administration of residues 1 to 123 of SEQ ID NO:2. This deficiency is made up for in the teachings of Spitler.

Spitler teaches methods of delivering antitumor vaccines with tumor associated antigens, including bladder antigens as well as known methods of delivering said tumor antigens to stimulate antitumor responses (see Summary of the invention). Spitler teaches that patients with cancer may have the cancer surgically excised (see column 10, lines 39-47) and then be given the tumor vaccine.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used SEQ ID NO:2 in a method of inducing an immune response in a bladder cancer patient in view of Au-Young and Spitler.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used SEQ ID NO:2 in a method of inducing an immune response in a bladder cancer patient in view of Au-Young and Spitler because Au-young teach the protein is in bladder tumor. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used SEQ ID NO:2 in a method of inducing an immune response in a bladder cancer patient in view of Au-Young and Spitler because Spitler teach methods

of treatment of cancers with administration of tumor associated antigens and in view of Au-young it would have been obvious to produce a method of inducing an immune response in a human because Au-young teach the antigen is associated with bladder cancer. In addition, it would have been obvious that the method would produce an antibody against SEQ ID NO:2.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

14. Claim 73 is rejected under 35 U.S.C. 103(a) as being unpatentable over Billing-Medel et al (WO 98/51805, published 11/98, IDS #8) and further in view of Spitler (U.S. Patent 5,738,867, filed 6/95).

Claim 73 is rejected because claim 73 is granted the priority date of 12/98 where the first instance of bladder cancer was observed to be disclosed in 09/203939.

Billing-Medel et al teach a protein PS116 which is identical to SEQ ID NO:2 of the instant application (see SEQ ID NO:25). Billing-Medel also teach that PS116 is associated with bladder cancer (see Figure 4). Billing-Medel does not teach a method of inducing an immune response in a bladder cancer patient by administration of residues 1 to 123 of SEQ ID NO:2. This deficiency is made up for in the teachings of Spitler.

Spitler has been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used SEQ ID NO:2 in a method of

inducing an immune response in a bladder cancer patient in view of Billing-Medel and Spitler.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used SEQ ID NO:2 in a method of inducing an immune response in a bladder cancer patient in view of Billing-Medel and Spitler because Billing-Medel teach the protein is in bladder tumor. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used SEQ ID NO:2 in a method of inducing an immune response in a bladder cancer patient in view of Au-Young and Spitler because Spitler teach methods of treatment of cancers with administration of tumor associated antigens and in view of Billing-Medel it would have been obvious to produce a method of inducing an immune response in a human because Billing-Medel teach the antigen is associated with bladder cancer.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

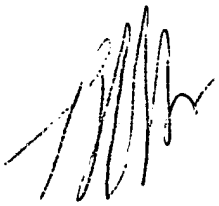
15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by

telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,



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